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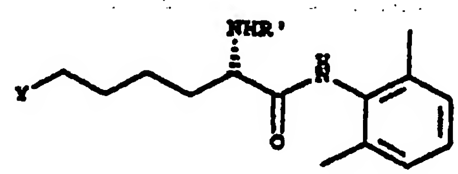
(54) Title: THE MANUFACTURE OF LEVOBUPIVACAINE AND ANALOGUES THEREOF FROM L-LYSINE

(57) Abstract

A novel compound of formula (X) is prepared from L-lysine, and converted to Levobupivacaine by cyclisation.



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THE MANUFACTURE OF LEVOBUPIVACAINE AND ANALOGUES THEREOF FROM L-LYSINE

Field of the Invention

This invention relates to a cost-effective process for the conversion, via diazotisation methodology, of L-lysine to a carboxanilide precursor of levobupivacaine and related compounds.

Background of the Invention

Compounds of formula **1** wherein R is a methyl, *n*-propyl or *n*-butyl group are widely used as local anaesthetics. Biological studies have shown that the (*S*)-enantiomers of such compounds (e.g. levobupivacaine wherein R is *n*-butyl) display lower cardiotoxicity than the corresponding racemates whilst maintaining the same anaesthetic potency, and are therefore more beneficial for clinical uses. Thus there is a requirement for efficient processes to manufacture compounds of formula **1** in the form of single enantiomers. The process embodied by the present invention employs a chirality pool approach to levobupivacaine, commencing from L-lysine, an inexpensive starting material which is readily available in bulk.

Although L-lysine has been converted through to optically enriched L-pipecolic acid and esters thereof by diazotisation and cyclisation reactions, cyclisation of an intermediate to form a piperidine-2-carboxanilide directly has hitherto not been reported. Furthermore, in the context of the present invention, these existing methods are hampered by an excessive number of steps required for manipulation of protecting groups in order to obviate Walden inversion at the carboxyl-bearing centre, which leads to the formation of D-pipecolic acid.

An additional benefit of the invention is the provision of unnatural amino acids of formula **2** with (*S*) configuration, which are important as pharmaceutical intermediates, e.g. for incorporation into physiologically active synthetic peptides. Compound **2a** is commonly prepared by a multistep synthesis of the racemate

commencing from dihydropyran followed by enzymatic resolution of an ester derivative (e.g. *p*-nitrobenzyl). This process in inefficient with respect to the number of steps required and by the fact that resolution produces up to 50% of an unwanted enantiomer. Diazotisation of L-lysine and derivatives thereof has been identified as an alternative strategy for the preparation of 2-amino-6-hydroxyhexanoic acid and derivatives thereof. However, such an approach has hitherto only been applied to the synthesis of compound **2c**, but this process, employing sodium nitroprusside, is low yielding (28%).

Copper complexation of lysine and similar amino-acids has been extensively used as a technique for temporary protection of the α-amino acid moiety, as disclosed by Ledger *et al*, Anstr. J. Chem. 18:933-5 (1965). This procedure facilitates selective transformation of the second amino group present in the side-chain, e.g. the attachment of a covalently-bonded amino-protecting group.

Summary of the Invention

This invention provdes a cost-effective process for preparing compounds of formula 1, wherein R is H or alkyl, from the inexpensive starting material L-lysine, using a chirality pool approach, and involving scission of the terminal C-N bond of L-lysine. In particular, the present invention provides a practical and economical process for the manufacture of levobupivacaine from L-lysine, which is exemplified in Scheme 1. This process involves the preparation of novel compounds of formula (X) as defined in claim 1; either R′ is a protecting group, in which case R is H in the product, which can then be alkylated as desired, or R′ is alkyl and corresponds to R as alkyl.

Description of the Invention

Formula (X), and other formulae used herein, refer to compounds that have at least predominantly the given stereochemistry. They are at least substantially free of their optical antipode, e.g. in at least 50%, more preferably at least 70% or 99%, enantiomeric excess.

According to the particular reactions shown in Scheme 1, the *α-N*-benzyloxycarbonyl derivative of L-lysine is initially (a) subjected to diazotisation in the presence of acetic acid to afford (*S*)-2-(benzyloxycarbonylamino)-6-acetoxyhexanoic acid (**2b**). Alternatively, Z may be any other blocking group, many examples of which are well known to the skilled man.

The next three steps of Scheme 1 proceed by way of novel compounds **3-5**: (b) Condensation with 2,6-dimethylaniline gives compound **3**; (c) cleavage of the *O*-acetyl group by methanolysis gives compound **4**; and (d) tosylation gives compound **5**. The OTs group shown in Scheme 1 is merely one example of many leaving groups which can be used and which are known to the skilled man. Examples are given in claim 2.

Finally, compound **5** is (a) subjected to hydrogenation in the presence of base to effect direct conversion to enantiomerically pure (*S*)2′,6′-dimethylpiperidine-2-carboxanilide **6**. Variants of this process include conversion of the *α-N*-benzyloxycarbonyl (or other blocked) derivative of L-lysine to compound **6** via alkyl halide derivatives of formula **7**. The conversion of compound **6** to levobupivacaine or other N-alkylated analogues can be carried out by methodology known to those skilled in the art, or as described in another Patent Application filed today, claiming priority from British Patent Application No. 9421478.0. Preferably, R is methyl, n-propyl, cyclopropyl or, most preferably, n-butyl.

A preferred aspect of the process summarised in Scheme 1 is the use of either sodium nitrite/sodium acetate/acetic acid or isoamyl nitrite/acetic acid as efficient reagent systems for the conversion of *α-N*-benzyloxycarbonyl or otherwise blocked L-lysine to the compound **2b**, by formation of a diazonium intermediate followed by solvolysis of this species or of the carbocation formed by loss of N_2. This discovery provides significant benefit over the prior art

process since the yields are much higher (60-87% of **2b** compared to 28% **2c**).

As a further feature of the invention, we have discovered that L-lysine can be cleanly and efficiently converted to (*S*)-2-amino-6-hydroxyhexanoic acid **2a** in a process (Scheme 2) involving sequential formation of bis(lysinato)copper, diazotisation-solvolysis to generate the novel copper(II) complex **8**, and cation-exchange to effect decomplexation. Diazotisation-solvolysis in such processes can be effected in aqueous media using either sodium nitroprusside at pH >10 or sodium nitrite, e.g. at pH <4.

More generally, NH_2 may be converted to any leaving group Y, e.g. halide, usually under anhydrous conditions, using known methodology. Depending on the stability of the metal complex, the reaction proceeds in one or more steps, to give a compound of the formula

$$Y-(CH_2)_4-CH(NH_2)-COOH$$

in optically-enriched form. The free amine may be blocked at this stage, as a reactant for use in Scheme 1.

Such processes are advantageous over conventional diazotisations of L-lysine, which give mixtures of products arising from unselective transformation of either one, and in some cases both, of the two amine groups present.

The following Examples illustrate the invention. Examples 1 to 5 illustrate respective steps in Scheme 1; Example 6 illustrates Scheme 2.

Example 1

A stirred solution of N^{α}-benzyloxycarbonyl L-lysine (6.33 g, 22.6 mmol) in acetic acid (150 ml) was treated with sodium acetate (1.85 g) and then sodium nitrite (1.56 g x 3) at 40°C. The reaction was stirred for 3 hours at 40°C, cooled and the bulk of the acetic acid was removed *in vacuo* and the residues partitioned between water (100 ml) and dichloromethane (100 ml x 3). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give compound **2b** a yellow oil (6.35 g, 87%).

Example 2

Isoamyl nitrite (6.1 ml) was added to a stirred solution of N^{α}-benzyloxycarbonyl L-lysine (6.34 g, 22.6 mmol) in glacial acetic acid (35 ml) at 22°C. The mixture was heated at 50°C for 12 hours, then volatile material removed by distillation *in vacuo* (last traces removed via formation of azeotopic mixtures with toluene) to give compound **2b** (4.38 g, 60%).

Example 3

A solution of compound **2b** (6.35g, 19.7 mmol) in dichloromethane (150 ml) was treated sequentially with 2,6-dimethylaniline and a solution of dicyclohexylcarbodiimide (4.89 g) in dichloromethane (10 ml) at 18°C. The reaction was stirred for 24 hours. The precipitate which formed was filtered and washed with dichloromethane (100 ml). The organics were concentrated *in vacuo* to give compound **3** as waxy solid. Without further treatment, this material was dissolved in MeOH (150 ml) and solid K_2CO_3 (9.57 g) was added. The reaction was stirred for 24 hours then filtered and evaporated to leave a waxy solid which was chromatographed on silica gel with 1.5:1 EtOAc:heptane to give compound **4** as a colourless solid (2.22 g, 28%).

Example 4

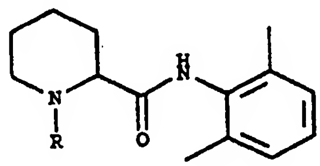
p-Toluenesulphonyl chloride (0.4 g) was added to a solution of compound **4** (0.60 g, 1.7 mmol) and pyridine (1.4 ml) in dichloromethane (5 ml) and stirred for 4 hours. Dilute hydrochloric acid (1 N; 10 ml) was added, and after stirring for 18 hours the mixture was extracted with dichloromethane (50 ml). The organic solution was washed with aqueous NaOH (1 N; 10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil which was chromatographed on silica gel eluting with 1:1 EtOAc:heptane. This gave compound **5** as a colourless oil (0.76 g, 81%) which slowly solidifies as the tosyl derivative.

Example 5

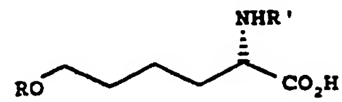
A mixture of compound 5 (0.76 g,1.4 mmol), Pd/C (0.076 g) and K_2CO_3 (0.47 g) in EtOH (15 ml) was placed under an atmosphere of hydrogen (balloon) and stirred vigourously for 3 hours. The reaction was filtered and the solids thoroughly washed with EtOH (5 ml). The combined filtrate and washings were concentrated *in vacuo* and the residue partitioned between dichloromethane (3 x 25 ml) and aqueous NaOH (1 *N*; 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give (*S*)-2′,6′-dimethylpiperidine-2-carboxanilide **6** as a colourless solid (0.284g, 87%), which was shown by chiral HPLC analysis to have an optical purity of >98%.

Example 6

A suspension of L-lysine (0.931 g, 5.1 mmol) and $CuCO_3.Cu(OH)_2$ (1.24 g, 5.6 mmol) in water (15 ml) was heated under reflux for 5 minutes then cooled and filtered. The pH of the filtrate was adjusted to 4 with 2M H_2SO_4. A solution of sodium nitrite (0.70 g, 10 mmol) in water (5 ml) was added dropwise over 10 minutes and the mixture was stirred at 24°C for 6 hours. Chelex 100 resin (40 g) was added to effect decomplexation. The resulting suspension was then filtered to give a solution of L-lysine (60%) and (*S*)-2-amino-6-hydroxyhexanoic acid **2** (30%).



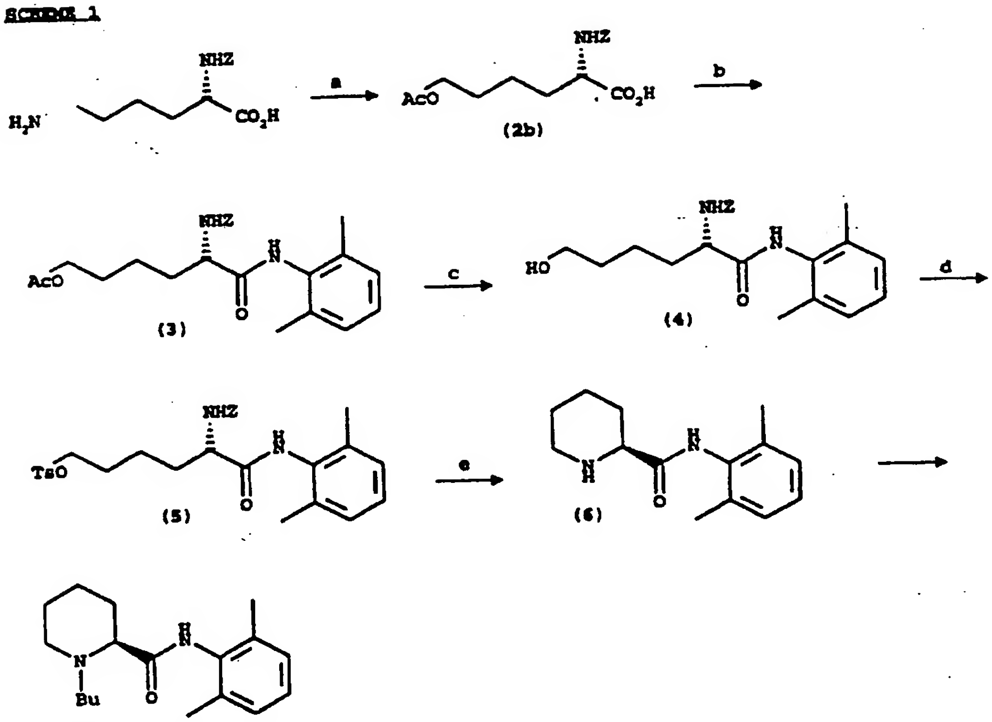
(1)



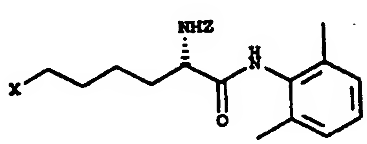
(2)

2a: R=R'=H
2b: R=Ac; R'=Z
2c: R=H, R'=Z

SCHEME 1

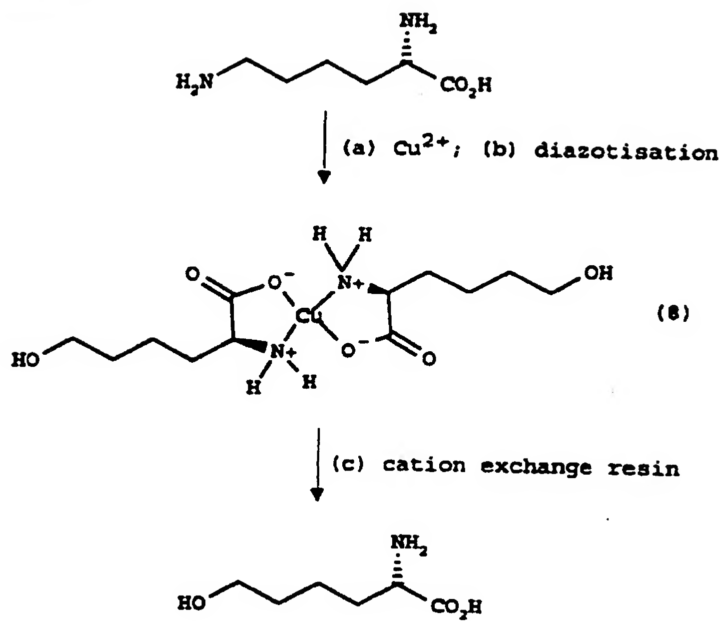


levobupivacaine



(7; X=Cl,Br,I,F)

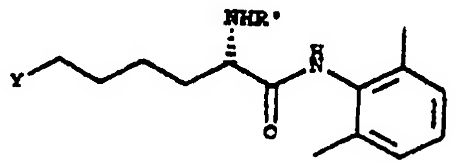
SCHEME 2


NH$_2$
H$_2$N
CO$_2$H
(a) Cu^{2+}; (b) diazotisation
H H
O
O$^-$
N+
OH
Cu
HO
N+
O$^-$
O
H H
(c) cation exchange resin
NH$_2$
HO
CO$_2$H

(8)

CLAIMS

1. A carboxanilide represented by formula X



(X)

wherein R′ is a removable amino-protecting group or alkyl, and Y is a leaving group.

2. A compound according to claim 1, wherein R′ is an amino-protecting group.

3. A compound according to claim 1 or claim 2, wherein Y is N_2^+, OH, O-acyl, -alkylsulphonyl, O-arylsulphonyl or halide.

4. A compound according to any preceding claim, wherein R′ is benzyloxycarbonyl.

5. A compound according to claim 4, wherein Y is acetoxy.

6. A process for the preparation of (*S*)-2′,6′-dimethylpiperidine-2-carboxanilide from L-lysine, which comprises the steps of conversion of L-lysine to a carboxanilide according to any of claims 1 to 5, and cyclisation to form a piperidine ring.

7. A process for the preparation of a carboxanilide according to any of claims 1 to 5, which comprises diazotisation-solvolysis of L-lysine.

8. A process according to claim 7, which comprises using sodium nitrite and sodium acetate in acetic acid.

9. A process according to claim 7, which comprises using isoamyl nitrite in acetic acid.

10. Use of a carboxanilide according to any of claims 1 to 5, or the product of a process according to any of claims 6 to 9, for the manufacture of levobupivacaine.

11. Use of a carboxanilide according to any of claims 1 to 5, or the product of a process according to any of claims 6 to 9, for the manufacture of ropivacaine.

12. A copper or other metal complex of (*S*)-2-amino-6-(Y-substituted)hexanoic acid, wherein Y is OH or a leaving group such as a halogen atom.

13. An aqueous solution of the complex according to claim 12.

14. A process for preparing (*S*)-2-amino-6-(Y-substituted)hexanoic acid, wherein Y is as defined in claim 12, which comprises converting L-lysine to bis(lysinato)copper or another metal complex, conversion of the terminal NH_2 group(s) to Y, e.g. by diazotisation-solvolysis, and cation-exchange to effect decomplexation.

15. A process according to claim 14, wherein diazotisation-solvolysis is effected using sodium nitroprusside at basic pH, preferably above 10.

16. A process according to claim 15, wherein diazotisation-solvolysis is effected using sodium nitrite at acidic pH, preferably below 5.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 95/02385

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/26 C07C271/22 C07C309/73 C07D211/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SYNTHESIS., 1982 STUTTGART DE, page 163 L. KISFALUDY ET AL. 'ONE-STEP SYNTHESIS OF L-PIPERIDINE-2-CARBOXYLIC ACID' cited in the application see the whole document ---	1-11
A	AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 18, 1965 MELBOURNE, pages 933-935, R. KEDGER ET AL. 'THE USE OF SEQUESTERING AGENTS IN THE PREPARATION OF EPSILON-L-LYSINE AND DELTA-L-ORNITHINE DERIVATIVES' cited in the application see the whole document -----	12-16

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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